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<b>(21) International Application Number:</b> PCT/EP90/00990 <b>(22) International Filing Date:</b> 19 June 1990 (19.06.90) <b>(30) Priority data:</b> 89201591.8 19 June 1989 (19.06.89) EP <b>(34) Countries for which the regional or international application was filed:</b> AT et al. <b>(71) Applicant (for all designated States except US):</b> AKZO N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GEERLINGS, Maurits, Willem [NL/NL]; Steenhoek 18, NL-6891 CG Rozendaal (NL). KASPERSEN, Franciscus, Michael [NL/NL]; Acaciaaan 13, NL-5384 BB Heesch (NL).		<b>(74) Agent:</b> HERMANS, Franciscus, Guilielmus, Maria; Postbus 20, NL-5340 BH Oss (NL). <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent)*, DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US. <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

**(54) Title:** RADIOIMMUNOTHERAPY USING  $\alpha$ -PARTICLES EMISSION**(57) Abstract**

The present invention relates to the use of Actinium or one of its daughters in radioimmunotherapy. Also provided are immunoconjugates comprising an isotope, a chelating agent and a slowly localizing antibody. The invention also includes pharmaceutical compositions comprising said immunoconjugates, as well as such compositions comprising one or more scavenging agents. The compositions according to the invention are particularly useful for the treatment of micrometastases in adjuvant therapy, as well as for treatment of localized tumors.

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### Radioimmunotherapy using $\alpha$ -particles emission

This invention generally relates to immunotherapy using radionuclides. More specifically it relates to immunotherapy using radionuclides which emit  $\alpha$ -particles (Helium-nuclei).

Radionuclides that emit  $\alpha$ -particles have a number of physical characteristics that make them attractive for radioimmunotherapy.

The range of an  $\alpha$ -particle with an energy of 5 to 8 MeV is in the order of 40 to 80  $\mu\text{m}$ , which limits their effectiveness to a range of several celldiameters from the decaying atom.

Within this range however, the cytotoxicity of  $\alpha$ -particles is extraordinary. This may be contributed to the high linear energy transfer (100 keV/ $\mu\text{m}$ ) and the high electrical charge of the particles. At doses of 100 to 200 cGy  $\alpha$ -radiation may be 5 to 100 times as toxic as  $\gamma$ - or  $\beta$ -radiation.

This invention also relates to a radio-immunoconjugate comprising a radionuclide which emits  $\alpha$ -particles, a chelating agent and a tumorspecific antibody.

Such a radioimmunoconjugate has been disclosed in Macklis et. al. (Science vol. 240 p1024-1026, 1988) wherein a  $^{212}\text{Bismuth}$  isotope is used, coupled to a monoclonal antibody by the cyclic anhydrid of DTPA (Diethylenetriamine pentaacetic acid), a derivative of the well-known chelating agent DTPA.

The monoclonal antibody described is directed against a murine antigen represented as Thy 1.2, which is present on the surface of both normal and malignant murine T-cells.

Bismuth isotopes have also been described in U.S. patent no. 4.454.106 for the purpose of radioimmunotherapy.

Another  $\alpha$ -particles emitting isotope mentioned for use in immunotherapy is  $^{211}\text{Astatine}$  (Bloomer et. al. Science vol. 212 p340-341, 1981).

$^{212}\text{Bismuth}$  has a physical half-life of 60.55 minutes and  $^{211}\text{Astatine}$  has a physical half-life of just over seven hours.

A short physical half-life like that of Bismuth requires a very fast extraction of the isotope from its source, a very fast chelation step (including the removal of adventitiously bound metal) and the extraction must be followed by immediate administration. Every hour delay between obtaining the isotope and administering it results in a dosage which is only half the intended dose.

It is therefore necessary that the source for radioactive bismuth is available in the direct vicinity of the patient. The source described for  $^{212}\text{Bismuth}$  is either  $^{228}\text{Thallium}$ ,  $^{224}\text{Radium}$ , or  $^{212}\text{Pb}$ . The first two decay chains involve a  $^{220}\text{Rn}$  isotope, which is a noble gas and may easily leak away. Most hospitals will not be equipped to house a source with such risks.  $^{212}\text{Pb}$  of course has a much too short physical half-life (10 hours) to enable a producer to achieve a good distribution.

<sup>211</sup>Astatine has a longer physical half-life than <sup>212</sup>Bismuth. It would perhaps be possible to locate the source for this isotope outside the hospital. However, Astatine is a halogen atom which behaves very similar to Iodine, including the well known drawbacks of accumulation in certain organs and tissues. Especially because <sup>211</sup>Astatine compounds are unstable in vivo (Int. J. Appl. Rad. Isotop. 32 p. 913 1981).

Apart from these drawbacks there is also the problem of obtaining sufficient quantities of the aforementioned isotopes, because their sources are available only in microgram quantities if at all.

The present invention provides a novel radio-immunoconjugate which includes a radionuclide which overcomes the previous mentioned problems.

Another problem arising in the field of radioimmunotherapy in humans is the availability of suitable antibodies. Murine antitumor antibodies which have been suggested, will, especially after several administrations, give rise to an immunereaction by the patient. Even fragments of these antibodies will eventually lead to this response.

The solution to this problem would be the use of human monoclonal antibodies, but these are not readily available.

A good method of obtaining human monoclonal antibodies has been disclosed in European Patent Application No. 0151030. However, this method tends to produce IgM-antibodies primarily.

A problem with IgM-antibodies is that they are fairly slow in reaching the site in the body where their antigens are located (the tumor). This may take from a day up to several days.

Therefore the normally used  $\alpha$ -emitters such as the earlier mentioned, will have decayed for the larger part when they reach their site of action.

The invention resides in a conjugate of  $^{225}\text{Actinium}$  or one of its daughters as a radionuclide and slowly localizing human- or humanized antibodies.

Slowly localizing antibodies are meant to include slowly localizing fragments of antibodies, or fragments which have been made slowly localizing by associating them with a carrier.

Among a list of others,  $^{225}\text{Actinium}$  has been suggested as a suitable  $\alpha$ -emitter (Monoclonal Antibodies Drug Dev.; Proceedings of the John Jacob Abel Symposium for Drug Dev., 1982, page 159-171).

The  $\alpha$ -emitter of interest according to the authors, is  $^{224}\text{Ra}$ .

The paper relates to mouse IgG-monoclonals or fragments thereof, which localize faster than human IgM-antibodies, but which will lead to an immuneresponse.

Furthermore, the authors did not try any  $\alpha$ -emitters in therapy, but only tried  $^{125}\text{I}$ -IgG-conjugates in a model system.

The conjugates with  $^{125}\text{I}$  did not lead to any improved results over unlabeled antibodies in their experiments.

Later on the authors turned from  $^{224}\text{Ra}$  with a half-life of approximately three days to  $^{212}\text{Bi}$ , which has an even shorter half-life.

In choosing  $^{225}\text{Actinium}$  a radionuclide is provided with a suitable physical half-life of approximately ten days.

This matches the localization time of human IgM-antibodies very well.

Furthermore a practically inexhaustible source is available in  $^{233}\text{Uranium}$ , which is abundantly stockpiled as an unused source of fuel for nuclear breeder reactors.

From  $^{233}\text{Uranium}$   $^{229}\text{Thorium}$  can be extracted, which can be used as an intermediate source (physical half-life 7340 years). Moreover, the decay chain of  $^{225}\text{Actinium}$ , represented below, includes four decays via an emission of  $\alpha$ -particles, without producing significant amounts of X-rays and no halogen atoms or noble gas isotopes.

This cascade may significantly increase the cytotoxic effect on the tumor cells.

However, upon the first decay the remaining isotope may be propelled away from the tumor (or into the tumor, for that matter!). This would result in emission of  $\alpha$ -particles in places far away from the tumor. The physical half-lives of  $^{221}\text{Fr}$  and  $^{217}\text{At}$ , as well as  $^{213}\text{Po}$ , are too short for these isotopes to wander far off, but the  $^{213}\text{Bi}$  has a physical half-life which may result in displacement of the isotope.

Therefore the present invention also provides a pharmaceutical composition comprising a radioimmunoconjugate including  $^{225}\text{Actinium}$  or one of its daughters as well as one or more scavenging agents.

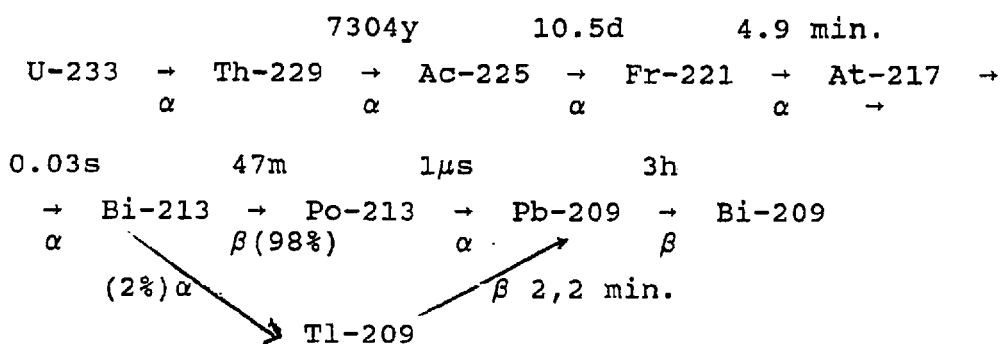
Scavenging agents are usually free chelating agents which may bind the wandering isotopes. In doing so they prohibit the isotopes to invade organs or tissues and improve the speed with which the isotopes are excreted.

The chelating agents used to bind Actinium or Bismuth, as well as the agents used as scavengers may be the usual chelating agents such as DTPA or derivatives thereof, PLED or its derivatives, EDTA or its derivatives, or crownethers or derivatives etc.



As scavengers EDTA, 2,3-dimercaptosuccinic acid and penicillamine are preferred.

Scheme. 1



An additional advantage of using  $^{225}\text{Ac}$  is that its compatibility with specific antibodies and chelating agents can be easily tested by substituting  $^{227}\text{Ac}$  for  $^{225}\text{Ac}$ .

$^{227}\text{Ac}$  is a commercially available  $\beta$ -emitter with a relatively long physical half-life, which, from a chemical point of view behaves similar to  $^{225}\text{Ac}$ .

The tumorspecificity of the antibodies used in the radioimmunoconjugates according to the invention is of course a very important parameter. The best results will be obtained with antibodies which bind to the surface of the tumor cells. Internalization is not necessary, because the kinetic energy of the  $\alpha$ -particles, as well as the rebound energy of the isotope is high enough to have a cytotoxic effect from the outside.

Suitable antibodies are those obtained by the method disclosed in European Patent Application No. 0151030.

The dose range over which the  $^{225}\text{Ac}$  can be used effectively without causing too many side-effects is highly dependent on the kind of therapeutic use which is intended. Presently the intended use will mostly be adjuvant therapy (right after surgery, in order to attack micrometastases) and treatment of localised tumors.

The invention will be illustrated in the following experimental part.

Experimental.

- 1a Extraction of Thorium-229 from Uranium-233, built up from Thorium-232 in thermal or epithermal neutron power reactors.

This exercise, mainly performed in different places in the world during the fifties, has led to a stock-pile of Uranium-233, intended as a fission material for thermal power reactors.

Pursuit of this development has been largely abandoned, at least for the time being. Throughout the years, substantial amounts of Thorium-229 did build up through alpha decay from Uranium-233 and can therefore be isolated from stock-piles. The extraction and purification chemistry is sufficiently known and does not need any further elaboration.

More than sufficient amounts of Thorium-229 are available in the world from this route to serve the cancer therapy market for the forthcoming thousands of years.

Thorium-229, obtained from this route, and because of its radio-active decay halflife in the order of 8000 years, will serve as a source material for a "cow" from which AC-225 can be extracted on a continuous or intermittent basis. One gram of Thorium-229 can be recovered by this means from about 10 kg of Uranium-233, 30 years of age.

- 1b Another means of obtaining Thorium-229 is irradiation of Radium-226 in a thermal high flux reactor for about 3 years. About 20 grams of Radium-226 is needed to obtain 1 gram of Thorium-229 by this route.

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Much chemistry has been developed in the period of the nineteen sixties and seventies, to enable the separation and purification of Thorium from Uranium, c.q. Thorium from Radium, etc.

Quite a lot of detailed literature is available.

Some major references are (amongst many others):

- I. Brandsstetz, Soviet Radiochem. 5, 660 (1963).
- Gmelin Handbook of Inorg. Chem. U, Vol. D4 (1983), and U, Vol. D3 (1982).
- Proceedings of Actinide/Lanthanide Separations, Honolulu 1984 (Ed. G.R. Chappin, World Scientific).
- A.T. Kandil, Radiochim. Acta 26, 63 (1979).

2. Using Thorium-229 as a "cow" for the production of AC-225.

The continuous or batch-wise separation of Ac-225 from Thorium-229 and decay products is a well-known, straight forward extraction procedure. Well-known extraction media/solvents are TTA, TBP, HDEHE and sodiumthiocyanide, with or without using  $\text{CCl}_4$  as a co-solvent.

These, but also a variety of other methods, have been extensively described in the literature during the 60's and the 70's.

One gram of Thorium-229 produces 100 microgram per year of AC-225, assuming a 100% net extraction yield. This is equivalent to 5 curies per annum of Ac-225  $\alpha$ -radioactivity.

Literature (a selection of a long list):

- P.C. Stevenson: "The Radiochemistry of the Rare Earths, Sc, Y and Ac, (US Report NAS-NS 3020 (1961))
- N.W. Kinley: Progr. Nucl. Energy, Ser. IX 8, 89 (1967)
- P.M. Eagle: Preliminary Report of the Actinium Separation Project, US-Report MLM-454 (1950).
- M. Allison, Nucleonics 12, 32 (1954)
- J. Tousset Thesis, French Report NP-13367 (1961)
- A.M. Poshausen, J. Inorg. Nucl. Chem. 16, 323 (1961)
- R.A. Day, J. Am. Chem. Soc. 72, 5662 (1950).

### 3. Radio-therapeutic effectiveness of MeV-range $\alpha$ -rays

The radiosensitivity of a population of tumor cells is often expressed by  $D_0$ , the inverse slope of the linear portion of the logarithmic survival curve. For  $\alpha$  particles the logarithmic survival curves and known values of radiobiological sensitivity (i.e., the  $D_0$  is known) the dose required to reduce the cell population to any level of cell survival can be computed from the equation:

$$D = - (D_0) (\ln S)$$

where  $S$  is the fraction of surviving cells (Humm and Cobb, J. of Nucl. Med., 31-1, 75 (1990)). Uniform distribution of the  $\alpha$  particle source materials through tumor material is assumed. Typical values of  $D_0$  for  $\alpha$  particles are between 50-100 rad. The estimated fraction of tumor cells surviving in an absorbed dose of 350 rad, for  $D_0 = 75$  rad, is 0.01 or 1%.

The following table, derived from the formula given above, gives the survival ratio of tumor cells (or for that matter any equally sensitive biological cells) as a function of different radiation doses:

700 rad	gives a survival ratio of 0.01%				
500 rad	"	"	"	"	0.1 %
350 rad	"	"	"	"	1 %
15 rad	"	"	"	"	82 %
10 rad	"	"	"	"	88 %
5 rad	"	"	"	"	93 %
1.5 rad	"	"	"	"	98 %

all assuming a value for  $D_0$  of 75 rads, as is generally thought to be the case for alpha ray doses.

Assuming a homogenous distribution of Ac-225 through a tumor mass, a tumor size large in comparison with the average penetration range of  $\alpha$ -rays through biological cell material (in the order of 75 microns at most), and a characteristic penetration range of radio-active decay recoil nuclei through the cell tissue of the order of 1000 Å, and furthermore taking into account that 4  $\alpha$ 's are emitted through the Ac-225 decay chain within a relatively short duration, it is assumed that the total  $\alpha$  decay-related energy is dissipated within the tumor mass. From that it can be calculated that 1  $\mu$ Ci of Ac-225 per gram tumor together with its daughters will then supply a dose of 750 rad of energy to the tumor material, inducing a killing ratio of 99,99% of tumor cells.

It depends on the size of a tumor to what extent the assumptions given above are fully true: the larger the tumor, the smaller the chance the Actinium is homogeneously distributed throughout the tumor before decay; the smaller the tumor, the larger the chance of

decay energy not fully absorbed by tumor cells. For example, it can be calculated that for an Actinium atom on the surface of a one-cell tumor, the amount of total decay energy generated being absorbed by the tumor cell will be in the order of only 250 rad per  $\mu\text{Ci}$  on a gram basis. Like always in pharmacology, also in the case of  $\alpha$ -radioimmunotherapy the challenge of supplying sufficient active material to those locations relevant for effectiveness of therapy, in comparison to body tissue at large, is the key for the size or the extent of the "therapeutic range". In the case of  $\alpha$ -emitting Ac-225 isotopes conjugated onto human monoclonal antibodies, the therapeutic range is solely determined by the nature and properties of the antibodies: their relative affinity to the tumor cell surface antigens for which they are destined in comparison with their affinity to other human body tissues, and the relative duration of the antibody-antigen bond in comparison with the average retention time of the antibodies by the other body tissue.

4. Affinity and clearance rate data of human monoclonal antibodies against colon tumor cell surface antigens.

Reference: M.G. Hanna, Jr. PhD, et al: "Development and Application of Human Monoclonal Antibodies", current status and future directions in immunoconjugates - University of Miami - School of Medicine, continuing education series, February 15-16, 1990.

Biotechnology Research Institute of Organon Teknika Corporation Rockville, MD 20850, developed human monoclonal antibodies of the IgM-type, with specific affinity for human colon carcinoma cells (cytoplasmic and cell surface determinants). These antibodies referred to as 28A 32 and 16.88 were labeled with Iodine-131 (5mCi/8  $\mu\text{g}$ ) and intravenously administered to patients with metastatic colorectal carcinoma. The

antibodies can be repeatedly and stably grown on a kg scale and repeated administration to the patients showed that they are not immunogenic.

Relevant for the present patent application are the observations made by radio-active imaging regarding the pharmacokinetic characteristics of these antibodies. Day to day scanning of the patients showed 5 to 7 days after intravenous administration. The average retention time in imaged nodules showed to be 17 days.

An important conclusion of these observations is that the retention time of conjugated antibodies in tumor tissue is at least 3 times as long as the average retention time in other body tissues.

In addition, prechirurgical pharmacokinetic studies were completed in several colon cancer patients and tumor versus normal colon ratios have been obtained for the human MAb 16.88. The results demonstrated tumor to normal tissue uptake ratios (liver metastases) of up to 10 to 1. Similar results were achieved by R.P. McCabe, et al (cancer research 48, 4348-4353, August 1, 1988) on colorectal cancer bearing nude mice, this time using Iodine-125-labeled antibody.

The conclusion is that, using such antibodies, an  $\alpha$ -ray dose to onco-colorectal cells in patients can be achieved in the order of a factor 25 or more higher than to body tissue in general of such patients.

In other words, an administration of over 350 rad of Ac-225-induced  $\alpha$ -rad energy per gram of tumor tissue can be achieved by the administration of about 15 rad/g to the overall body tissue. This implies that an administration of Ac-labeled monoclonal antibody causing 99% kill of tumor cells will only induce an 18% kill of non-tumor tissue cells.

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On this basis, and recalling that  $1\mu\text{Ci}$  of Ac-225 delivers 750 rad of radiation energy to one gram of biological tissue, such a "therapeutic range" for a patients of 75 kg of body weight can be achieved by post-operative administration of 1.5 mCi of Ac-225-conjugate. This corresponds with a "therapeutic dose" of about 30 ng of Actinium-225. p.m.: This implies that 100,000 patients per annum can be treated with such a therapeutic dose on the basis of 3 mg per annum of Ac-225, which, with an overall efficiency of about 30%, can be continuously extracted from a "cow" containing 100 grams of Thorium-229.

Any improvement in selectivity of antibody above the figures given in this example will directly, in proportion, reduce the need of the size of the Thorium-229 "cow".

#### Example Ia

(4-isothiocyanatobenzyl)-DTPA 2,5 mg/ml is dissolved in PBS (0,066 M phosphate/ 0,13 M NaCl pH=7,2-7,4) and 10  $\mu\text{l}$  of this solution are added to the monoclonal antibody dissolved in PBS (1 mg/ml). The mixture is stirred for two hours at ambient temperature. Free chelating agent is removed by size exclusion filtration over sephadex G50 (25 cm x 0,5 cm) in PBS. The chelator-antibody conjugate is stored in PBS at 4 °C in a concentration of 0,5 mg/ml.



Example Ib

The volume of the  $^{225}\text{Ac}$  as eluted from the  $^{225}\text{Ac}$  generator (100  $\mu\text{Ci}$ ) is reduced to 50  $\mu\text{l}$  and the pH is adjusted to 5 with  $\text{NaH}_2\text{phosphate}$ -solution (0,1 M). The resulting solution is incubated immediately with (benzyl) DTPA-conjugated antibody: 250  $\mu\text{g}$  in 0,5 ml PBS for 15 minutes. DTPA (1 mg) in 10  $\mu\text{l}$  PBS are added and the mixture is incubated for another 5 minutes. The mixture is subjected to size exclusion chromatography over sephadex G50 (10 x 2 cm) and the void volume (yield 80%) gives  $^{225}\text{Ac}$ -benzyl-DTPA-monoclonal antibody.

Example II

A solution of  $^{225}\text{Ac}$  (100 $\mu\text{Ci}$ ) as obtained from the cow (in HCl) was evaporated to dryness under a gentle stream of nitrogen. It was dissolved in 100  $\mu\text{l}$  PBS buffer. To this solution 500  $\mu\text{l}$  antibody (16.88) conjugated to benzyl DTPA (2mg/ml) was added and after 10 minutes incubation at room temperature the mixture was chromatographed over a Sephadex<sup>R</sup> PD10 column using PBS as element. The high molecular weight fractions were collected and used (as such) or after concentration by centrifugation over Centricon<sup>R</sup> pretreated with BSA.

## Claims

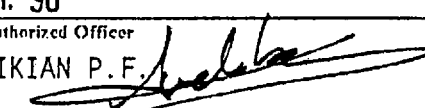
- 1) A radioimmunoconjugate, comprising a radionuclide which emits  $\alpha$ -particles, a chelating agent and a tumorspecific antibody, characterized in that the radionuclide is an  $^{225}\text{Actinium}$  isotope, or one of its daughters and that the antibody is a slowly localizing antibody.
- 2) A radioimmunoconjugate according to claim 1, characterized in that the antibody is an IgM-antibody.
- 3) A radioimmunoconjugate according to claim 1 or 2, characterized in that the antibody is a human-, or a humanized antibody.
- 4) A radioimmunoconjugate according to claim 3, characterized in that the antibody is monoclonal antibody 16.88.
- 5) A radioimmunoconjugate according to claim 3, characterized in that the antibody is monoclonal antibody 28A 32.
- 6) Pharmaceutical composition comprising a radioimmunoconjugate according to any of the foregoing claims.
- 7) Pharmaceutical composition according to claim 6, characterized in that it comprises one or more scavenging agents.

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 90/00990

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K43/00		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	INTERNATIONAL JOURNAL OF RADIATION APPLICATIONS AND INSTRUMENTATION PART A vol. 37, no. 8, March 1986, GB pages 789 - 798; BROWN I.: "Astatine-211: Its Possible applications in cancer therapy" see the whole document ---	1-7
A	HEALTH PHYSICS. vol. 35, no. 1, July 1978, OXFORD GB pages 21 - 24; DELIKAN O.: "Preparation of 224Ra for Therapy of ankylosing spondylitis" see the whole document ---	1-7
A	EP,A,151030 (LITTON BIONETICS) 07 August 1985 see the whole document (cited in the application) ---	1-7
<p><sup>10</sup> Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
16 OCTOBER 1990	16. 11. 90	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	AVEDIKIAN P.F. 	

SA 38054

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-151030	07-08-85	AU-B- 589351	12-10-89
		AU-A- 3799285	08-08-85
		AU-A- 4736789	03-05-90
		JP-A- 60260597	23-12-85
		US-A- 4828991	09-05-89
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